

REMARKS

As a threshold matter, Applicant want to thanks the Examiner for providing Applicant the opportunity to discuss the issues raised in the Final Office Action in a telephonic interview held on June 3rd, 2003. During the interview, Applicant sought clarification of the Examiner's statements in paragraphs 2, 3, and 4 at page 6 of the Final Office Action made in response to Applicant's arguments filed on November 2, 2002, and in particular for the Examiner's statements regarding the teachings of Balazs and assertions of general knowledge in the art under paragraph 2, the teachings of Spiro under paragraph 3, and the assertion that certain features of Applicant's invention are not recited in the claims in paragraph 4. No agreement was reached, and Applicant's complete response is now presented in its entirety in this submission.

Also, Applicant kindly requests the Examiner to review the art cited in Form 1449 first submitted in an Supplemental Information Disclosure Statement on November 4, 2002 but which was not matched with the file record and which applicant has resubmitted on March 13, 2003 following notification by the Examiner in the outstanding February 12, 2003 Final Office Action. Applicant also kindly request review of the art cited in Form 1449 concurrently submitted herewith as a Supplemental Information Disclosure Statement under §1.97(b)(4). The reference Rhee (US 5,510,418) teaches the use of activated dicarboxylic molecules containing a PEG core to form conjugates with glycosaminoglycans.

Claims 1-23 are currently pending in this application. Claims 1, 5, 7, and 9 have been amended, and claims 21 to 23 have been added. Support for the claim amendments can be found in the specification at least as follows: support for amendment to claim 1, 5, 9 and new claims 21-23 can be found at least at page 5, lines 11 to 15 and 18 to 27, and from page 7, line 10 to page 8, line 8. Applicant believes that these amendments do not introduce new matter.

Rejection Of Claims Under 35 USC §102:

1. Claims 1-4 are rejected over Balazs as being allegedly anticipated by Balazs's disclosure of mixtures of polyethylene oxide and hyaluronic acid. Applicant has

amended independent claim 1 to now recite that, in the mixture, the polymerizable macromer comprises "at least a polyalkylene glycol region and at least one or more chemically reactive groups which react spontaneously or under the influence of activating conditions to form polymeric structures." Applicant respectfully submits that the amended claims are free of the cited prior art.

In maintaining this rejection over Applicants prior argument and amendment, the Examiner asserted at page 6 of the action that "it is well known that PEO can be reacted with functional groups and polymerized by photopolymerization or in presence of an initiator." Applicant respectfully traverses the examiner's statements to the extent they are maintained to the present claims for failing either to cite to a reference exemplifying the knowledge in the art or to take official notice. *Dickinson v. Zurko*, 527 U.S. 150, 50 USPQ2d 1930 (1999).¹ Furthermore, the reliance on facts or knowledge not contained within the Balazs reference is inappropriate for a rejection under section 102(a). Applicant respectfully requests that the Examiner identify the sections of the Balazs reference that teaches that the PEO of Balazs can be modified as stated by the Examiner. As detailed below, Applicant believes that Balazs does not provide such teaching and thus respectfully requests that this rejection be withdrawn.

Balazs only discloses compositions of polyethylene oxide (PEO) and hyaluronate. In contrast Applicant claims compositions of a PAG-interacting polymer and a polymerizable macromer having at least one polyalkylene glycol region and at least one or more chemically reactive groups which react spontaneously or under the influence of activating conditions to form polymeric structures. Such polymerizable macromer differs from PEO in that the PAG represents only a region of the macromer molecule as the macromer also contains groups capable of polymerizing, while PEO of Balazs is a stable, non-reactive large molecule. Therefore, Applicant submits that Balazs does not anticipate the claims as amended. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

¹ see also USPTO internal circular letter from Deputy Commissioner for Patent Examination Policy, Stephen G. Kunin, to Patent Examining Corps dated February 21, 2002 on "Procedures for Relying on Facts Which are Not of Record as Common Knowledge or for Taking Official Notice."

2. Claims 1-4 and 7 are rejected as allegedly being anticipated by Spiro. Applicant respectfully submits that Spiro does not anticipate the present claims.

Applicant claims compositions of matter that are mixtures of at least two components, a macromer containing PAG regions and chemically reactive groups which react spontaneously or under the influence of activating conditions to form polymeric structures and a PAG-interacting polymer. In contrast, Spiro teaches conjugates and mixtures for their preparation in which the conjugate is formed from the oxidation of hyaluronic acid (HA) and a sulfated polysaccharide (SP) and their subsequent reaction to a diamino-terminated polyethylene oxide (PEO diamine) to form a HA conjugated to SP wherein the components HA/PEO/SP are covalently bonded to each other to form a discrete conjugate. Because the components in the conjugates are covalently bonded, Spiro does not teach mixtures as claimed by applicants.

Furthermore, Spiro does not teach mixtures as presently claimed because even the precursor mixtures of Spiro do not contain the macromer of the present claims. In Spiro, the amino groups in the PEO-diamine precursor component, while capable of reacting with the activated HA component to form a HA-PEO-amine or HA-PEO-SP conjugate, is not capable of forming polymeric structures as claimed. At best, the amino groups form a Schiff base or an amide (depending on the corresponding activating group on the HA/SP molecule, the aldehyde or the activated carboxyl group, respectively)-i.e. the amino group in the PEO-diamine of Spiro does not make this molecule a macromer. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

3. Applicant respectfully submits that the present claims are also patentable over Rhee (US 5,510,418) for reasons similar to those presented above distinguishing the claimed compositions and methods from the teachings of Spiro.

Rejection Of Claims Under 35 USC §103(a):

1. Claims 1-20 are rejected as being allegedly obvious over the teachings of Sawhney in view of Balazs. Applicant respectfully submits that the amended claims are patentable over the cited combination of references as neither reference teaches the

required motivation to combine the teachings of one with the teachings of the other, and Applicant demonstrated unexpected results.

Applicant submits that Sawhney does not teach or suggest compositions as presently claimed. The Examiner properly noted that, while Sawhney discloses PAG macromers, it does not teach PAG-interacting polymers. Sawhney does not suggest a need for increasing the viscosity of the macromer solutions, nor is Sawhney concerned in evaluating the viscoelastic properties of the macromeric solutions. Therefore Sawhney lacks the necessary motivation to combine its teaching with Balazs's to arrive at the presently claimed compositions.

As stated above, Applicant reiterates that Balazs also does not teach or suggest compositions as presently claimed. Balazs only studied the viscosity of mixtures of PEO and HA. It does not teach or suggest any modification to be made on the PEO to increase the viscosity of the mixtures, nor does it suggest a need to make such modification. Yet Balazs does not show properties of compositions with other interacting polymers.

Absent a clear motivation in the cited art to combine the references, the combination is inappropriate as relying on hindsight from Applicant's own teachings. Accordingly, for this reason alone, this rejection should be withdrawn.

Even when combined, Sawhney and Balazs do not teach or suggest the presently claimed compositions. Applicant submits that the claimed compositions present unexpected viscoelastic characteristics, which render the compositions more desirable for implantation. These viscoelastic properties could not have been foreseen even in view of the teachings of Balazs and Sawhney. In particular, unexpected results from Applicant's compositions can be clearly seen (table below) from a comparison of viscosity (η) in function of the shear rate plotted in Figure 2 (claimed composition) and Figure 6 (comparative data) corresponding to compositions prepared according to Examples 4 and 8 respectively.

Viscosity: η (cP)	Shear Rate (RPM)					
	0.5	1	1.5	2	4	10
0.3% HA (2MDa)	160	145	(~130)	125	(<125)	(<125)
5% PEG (35KDa)	6	6	6	6	6	6

5% Macromer (20KTLA)	57	57	57	57	57	57
5% PEG + 0.3% HA	270	(~ 200)	190	(<190)	(<190)	(<190)
$\eta_{(5\% \text{ PEG} + .3\% \text{ HA})} / \eta_{(.3\% \text{ HA})}$	1.7	~1.4	~1.4	--	--	--
5% Macromer + 0.3% HA	~1050	~950	~850	~790	~600	~400
$\eta_{(5\% \text{ Macromer} + .3\% \text{ HA})} / \eta_{(.3\% \text{ HA})}$	6.5	6.5	6.5	6.3	--	--

Addition of HA to the solution of macromer increases the viscosity by a factor of 6 or more (see last row in table above). In comparison, the addition of HA to solution of PEG (having a similar molecular weight (~35KDa) as the PEG region of the macromer (20KDa)) increases the viscosity modestly by one and half fold (see 5th row in table above). Thus applicant has shown compositions that present an increase in viscosity four times higher (6/1.5) than the compositions similar to those of Balazs. This increase in viscosity is yet superior to the one observed by Balazs, as seen in Fig 2, which shows an increase in viscosity less than three-fold for a yet much larger PEG molecule (2MDa) and 0.2% HA.

Surprisingly, this increase in viscosity for the composition of this invention is observed to be two times (6/3) higher than the one observed by Balazs, even though the molecular weight of the macromer (~20KDa) is about 100 times smaller than the PEO of Balazs (2MDa); whereas a lower rate of increase in viscosity is observed, i.e. one half lower (1.5/3) for small PEO (35KDa) compared to the large PEO (2MDa) of Balazs.

Therefore, the observed advantageous increase in viscosity in the composition of this invention is unexpected in view of the cited prior art. Accordingly, applicant submits that the claimed compositions and methods are unobvious over the cited prior art and are therefore patentable.

Furthermore, the compositions of the present invention not only have an extremely high viscosity at low shear rate, they also have a substantial decreased viscosity, by more than half, under high shear rate, permitting the compositions to be easily injected to the desired site of implantation by needle or catheter and yet regain viscosity at the site of implantation. Balazs is silent on the desirability of these viscoelastic properties, as well as on the behavior under shear of its compositions; indeed

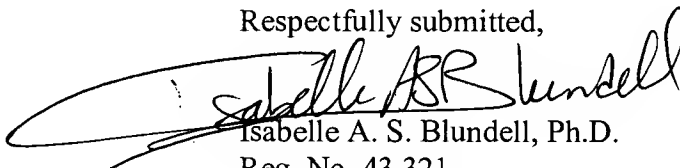
Balazs only concerns cosmetic compositions for topical application wherein behavior under shear such as shear thinning is not a critical property.

Accordingly, because the cited combination fails to teach or suggest the claimed compositions, Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

Applicant believes that all the issues raised in the Final Office Action have been addressed in conformity with the statutory requirements and respectfully submits that the aforementioned amendments and remarks place this application in condition for allowance.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Isabelle A. S. Blundell', is written over the typed name.

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